REMARKS

Applicants recently contacted Examiner Collins to discuss the propriety of the Final Office Action issued on May 21, 2003. Applicants raised the issue that the Final Office Action was seriously deficient in substantiating the position of the Patent Office with respect to each of the substantive rejections. Examiner Collins discussed Applicants' concerns with supervisory examiner, Amy Nelson. Following this discussion, Examiner Collins contacted the undersigned and invited Applicants to file an amendment after final for reconsideration by Examiners Collins and Nelson. Applicants appreciate the Examiner's offer to review and reconsider the case.

Claims 15, 17-27 and 28-92 are pending. Claims 15-20, 23-27, 29-34, 39-41, 66 and 74 have been amended while claim 92 has been added. The amendments are amply supported by the specification and raise no issue of new matter nor raise issues requiring further search. The Amendments have not been made to obviate prior art. The amendments are minor in nature involving mainly repositioning of claim limitations to further emphasize limitations that Applicant has long asserted are material to the claim.

REJECTION UNDER 35 U.S.C. § 112

Applicants respectfully traverse the rejection of claims 29-30, 48-50 and 86-88 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement with regard to the phrase "at least a portion of a heavy chain constant region." As a preliminary matter, it is noted that the phrase in question is also present in claims 77-79.

The proper standard for determining compliance with the written description requirement of 35 U.S.C. § 112, first paragraph, is whether the specification reasonably conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. *See* MPEP § 2163.02 (citing *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985)). The subject matter of the claimed invention need not be described literally in the specification in order to satisfy the requirements of 35

U.S.C. § 112, first paragraph. *Id.* In a careful analysis of the written description requirement provided by Patent and Trademark Office in its *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112 ¶1, "Written Description" Requirement*, it is stated that an adequate written description "may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention." 66 Fed. Reg. 1099, 1105 (2001) (emphasis added).

According to the Examiner, the basis for sustaining the written description rejection in the Final Office Action mailed May 21, 2003 was that "engineered immunoglobulins are neither disclosed nor exemplified in the specification." Office Action 5/21/03, page 3. As will be seen below, this view is unsupported and contradicted by overwhelming evidence to the contrary.

It is respectfully submitted that the phrase at issue "at least a portion of a heavy chain constant region" must be read in the context of the claims as a whole, which is directed to a method of passive immunization by administering an **"antigen-specific immunoglobulin."** The two phrases properly read together would be understood to mean an antigen specific immunoglobulin where the heavy chain includes at least a portion of the heavy chain constant region. When understood in the proper context, the phrase at issue cannot be construed, as alleged by the examiner, to encompass polypeptides "having as few as one amino acid." Office action 11/19/02. It is commonly known that an "antigen-specific immunoglobulin molecule" (or immunologically active fragment) by its very nature has a complete or nearly complete variable region, which typically constitutes about 100 or so amino acids.

Written description in the specification for "at least a portion of a heavy chain constant region" can be found, for example, at page 10, line 27-33 (emphasis added).

> Immunoglobulin product: **A polypeptide, protein or multimeric protein containing at least the immunologically active portion of an immunoglobulin heavy chain and is thus capable of specifically combining with an antigen**. Exemplary immunoglobulin products are an immunoglobulin heavy chain, immunoglobulin molecules, substantially intact immunoglobulin

> molecules, **any portion of an Immunoglobulin** that contains the paratope, including those portions known in the art as Fab fragments, Fab' fragment, $F(ab')_2$ fragment and Fv fragment.

Reference in the above to "at least the immunologically active portion of an immunoglobulin heavy chain" is an implicit reference to heavy chain variable regions that have any number of constant region residues. This language demonstrates that any and all fragments were contemplated, limited only by the requirement that the fragment be "immunologically active." The exemplied (i.e. non limiting) examples include Fab' and Fab'_2, which have CH1 domain and part of the hinge region or basically about 1/3 of the constant region heavy chain amino acids, while the Fv fragment has a heavy variable region and no constant region amino acids. Thus, the description in the specification shown above clearly contemplates immunoglobulins with heavy chains that have any number of constant region amino acids from zero to about 1/3 of the constant region residues in the exemplied non-limiting embodiments.

Additional written description for "at least a portion of a heavy chain constant region" also can be found at page 3, lines 1-6 (emphasis added) of the specification.

> One of the most useful aspects of using a recombinant expression system for antibody production is the ease with which the antibody can be tailored by molecular engineering. **This allows the production of antibody fragments and single-chain molecules, as well as the manipulation of full-length antibodies**. For example, a side [sic] range of functional recombinant-antibody fragments, such as Fab, F_v, single-chain and single-domain antibodies, may be generated.

This passage indicates that recombinant expression makes possible the production of a variety of antigen-specific immunoglobulins including those known from proteolytic processing (e.g., Fab) and those known only by recombinant expression of light and heavy chain variable regions (e.g., single chain antibodies). The word "including" indicates that other molecules with portions of a heavy chain constant region were contemplated. The above cited written description from the application directly contradicts the examiner's unsupported assertion that "engineered immunoglobulins are neither disclosed nor exemplified in the specification." Office Action 5/21/03, page 3.

Furthermore, there is no question that the ordinary skilled artisan would have understood from the evidence above that the application contemplates plant expression of a variety engineered immunoglobulin forms and not solely those known previous to genetic engineering techniques as alleged by the Examiner. This is evidenced by the state of the art as of the earliest filing date of the instant application. For example, U.S. Patent no. 4,816,567 to Cabilly et al., filed April 8, 1983, describes the use of recombinant DNA technology to express antibodies that have less than a full length heavy or light chain (Summary of the Invention; emphasis added).

> The invention relates to antibodies and to non-specific immunoglobulins (NSIs) formed by recombinant techniques using suitable host cell cultures. . . .
>
> Finally, either the light chain or heavy chain alone, **or portions thereof**, produced by recombinant techniques are included in the invention and may be mammalian or chimeric.

Cabilly also teaches recombinant expression of any and all immunologically active fragments by referring to expressing "at least the variable domain" of light and heavy chains.

U.S. Patent No. 4,704,692 to Ladner (cited on page 28 lines 5-13 of the instant application) teaches that recombinant methods can be used to express unique fragments of immunoglobulins in which terminal amino acids at the N- or C-terminus of the variable region of light or heavy chains are removed as part of the strategy for linking the chains with a peptide linker to form a single chain Fv fragment. Such antibody fragments would be immunologically active while comprising less than a full length variable domain and no constant domains.

Schwartzbaum et al. (Eur. J. Immunol., vol. 19(60, 1015-1023; 1989; see Exhibit A to the Amendment filed 2/19/03) used molecular biology techniques to construct IgE antibodies with deletions in either the $C_\varepsilon 4$ and $C_\varepsilon 3$ constants domains (see abstract). Similarly, Bettler et al. (PNAS, 86:7118-7122, 1989; see Exhibit B to the

Amendment filed 2/19/03) describes preparation of a large number of IgE constant domain deletion mutants (see Fig. 2).[1]

The existence of an adequate written description for the present claims is also consistent with the PTO's recently proposed "Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112(1) 'Written Description' Requirement" ("Revised Interim Guidelines"; 64 Fed. Reg. 71427, Dec. 21, 1999). The Revised Interim Guidelines state that determining whether an inventor is in possession of the claimed invention "is a conclusion reached by weighing many factual considerations, which "include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." As already discussed, extensive structural and functional information and correlation of structure with function was known about immunoglobulins. In addition, the level of skill in the art was high as indicated by the extensive publication history in antibody engineering, much of this knowledge being more than 20 years old. Finally, the patent specification contains an extensive description of how to make and use the claimed invention. Thus, the factual considerations in the instant case clearly support the existence of an adequate written description.

In view of the foregoing, Applicants respectfully submit that the inventors were in fact in possession of the invention which encompasses the phrase "at least a portion of the heavy chain constant region." Thus, as the written description requirement of 35 U.S.C. § 112, first paragraph, has been met, Applicants respectfully request that the rejection be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 102 OVER STOLLE

The rejection of claims 13, 15-27, 29-65 and 83-91 under 35 U.S.C. § 102(b) as being allegedly anticipated by Stolle et al., (U.S. 4,748,018) is respectfully traversed.

[1] These mutants were expressed as Fc fragments.

In order to anticipate a claim, a single prior art reference must provide each and every element set forth in the claim. *In re Bond*, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990). *See also*, MPEP §2131. The Examiner bears the initial burden of establishing a *prima facie* case of anticipation. Only once that *prima facie* case has been established does the burden shift to the applicant to rebut the *prima facie* case. *See, e.g., In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997).

The basis for the rejection, as best as Applicants can determine, is that the Examiner believes that the stated requirement for the immunoglobulin to be obtained from plant cells that contain the specified nucleic acids is not a material limitation of the method. Following the Examiner's logic, one could infringe the claim by administering immunoglobulin obtained from a conventional source such as the serum of an animal.

The Examiner's claim interpretation is at odds with accepted tenants of claim construction. The claims are to be read as a whole and the words are to be given their ordinary and custom meaning unless the prosecution history or the specification indicate otherwise. MPEP 2111.01. The claims also should be read in the context of the patent specification in which they arise. See Glaverbel Societe Anonyme v. Northlake Marketing & Supply, Inc., 45 F.3d 1550 (C.A.Fed.,1995).

Furthermore, every word in a claim must be taken into consideration. Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1248, 48 USPQ2d 1117, 1120 (Fed.Cir.1998) ("the claims define the scope of the right to exclude; the claim construction inquiry, therefore, begins and ends in all cases with the actual words of the claim."). "All the limitations of a claim must be considered when weighing the differences between the claimed invention and the prior art in determining obviousness of a process or method claim." MPEP 2116.01 (emphasis added); see also unpublished BPAI decision in In re Vandenbergh et al. WL1771384 (BAPI 1996), (applying the "all limitations" requirement of MPEP section 2116.01 to a rejection based on anticipation; see Exhibit C to the Amendment filed 02/19/03).

When read as a whole, the requirement for obtaining the antigen specific immunoglobulin from plant cells and the specified requirements of such cells cannot be understood as anything other than a material limitation of the method. The plant cell source is stated in all cases as a goal of the method. The preamble of Claim 92 is shown below as exemplary.

> A method of passively immunizing a human or non-human animal subject against a preselected antigen using an immunoglobulin molecule produced in transgenic plants, said method comprising

Furthermore, the plant source limitation for the antibody is prominent in the body of the claim, leaving no doubt of its materiality to the method. Subpart (a) of claim 92 shown below is exemplary..

> (a) obtaining a source of antigen-specific immunoglobulin from transgenic plant cells producing antigen specific immunoglobulin, said plant cells containing nucleotide sequence encoding an immunoglobulin heavy chain polypeptide and an immunoglobulin light chain polypeptide wherein said nucleotide sequences also encodes a leader sequence for each polypeptide wherein each leader sequence forms a secretion signal that is cleaved from each of said immunoglobulin heavy chain and light chain polypeptides following proteolytic processing; and

There is nothing in the specification or the claims that supports the Examiner's assertion that the plant cell source requirement is a mere characteristic of an immunoglobulin and not a material limitation of the method. The claims are directed to methods of passive immunization using antigen-specific immunoglobulin obtained from transgenic plants. As such, no reasonable interpretation of the claims could reduce the prominent plant source limitation to mere non-material verbiage as asserted by the Examiner.

In view of the foregoing, Applicants respectfully submit that because the plant source limitation is material the claims are not anticipated by Stolle et al. Applicants respectfully request that the rejection be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 103 OVER GOODMAN AND DÜRING IN VIEW OF STOLLE

Applicants respectfully traverse the rejection of claims 13, 15-27, 29-65 and 83-91 as allegedly being unpatentable over U.S. 4,956,282 ("Goodman") and the doctoral dissertation by Klaus During ("the During dissertation") in view of Stolle et al. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness.

To establish a *prima facie* case of obviousness, three criteria must be met: there must be some motivation or suggestion, either in the cited references or in knowledge available to the ordinarily skilled artisan, to modify or combine the references; there must be a reasonable expectation of success in combining the references; and the references must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991) See also MPEP §2143.

For obviousness to be present, the combination of art must enable the claimed subject matter. The prior art should not be viewed in a vacuum. Rather, it must be viewed with the perspective of the ordinary skilled artisan at the time the invention was made. See Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1143 (C.A.Fed.,1985) ("Those charged with determining compliance with 35 U.S.C. § 103 are required to place themselves in the minds of those of ordinary skill in the relevant art at the time the invention was made, to determine whether that which is now plainly at hand would have been obvious at such earlier time. The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time.").

Recent History of the Rejection

In the prior non-final Office Action mailed November 19, 2002, the Examiner offered several reasons that allegedly supported the rejection including 1) that the plant cell source limitation for the immunoglobulin was not a material limitation (page 6), and 2) that the Lerner declaration need not be considered because it was not commensurate in scope with the claims. These alleged basis for the rejection were addressed in Applicants'

Amendment of February 19, 2003. In particular, pages 10 and 11 of Applicants' February Amendment addressed the Examiner's mistaken belief that the Lerner declaration was not commensurate with the claims. Applicant provided, *inter alia* a declaration by the inventor, Andrew Hiatt, which demonstrated that antigen specific immunoglobulin fragments require processing and assembly in cells, as does full length immunoglobulin.

In the Final Office Action of May 21, 2003, the examiner withdrew the argument that the Lerner declaration was not commensurate with the claims. Page 7. Thus, besides the examiner's position that the plant source limitation is not a material limitation of the claimed methods, the only basis offered to support the obviousness rejection is the Examiner's belief that "both the During and Goodman references teach the production of antibodies in plant cells, notwithstanding the criticism set forth in Lerner." Page 7.

It is respectfully submitted that the present reasoning upon which the rejection is based is insufficient to sustain the obviousness rejection. As addressed extensively above, there is no proper reading of the claims that would cause the plant source limitation to be understood as anything other than an absolute requirement of the method. Once the issue of materiality is removed, there is nothing left to support the rejection except the examiner's personal belief that concerns raised by the Lerner Declaration are insufficient to overcome the alleged teaching by During and Goodman for expression of immunoglobulin in plants.

The rejection is clearly deficient because it is merely conclusory; It offers no rationale for why the criticisms of the Lerner declaration have been deemed insufficient by the Examiner. The declarant, Dr. Richard Lerner, is an expert in the field of immunology. This fact has not been challenged by the examiner. Dr. Lerner examines the state of the art at the relevant time period from the view of one of ordinary skill and demonstrates that there was a prejudice in the art against the possibility of expressing antigen-specific immunoglobulin in plants. This fact also has not been challenged by the Examiner. Dr. Lerner conducted and extensive analysis of the experimental results that underlie During's claim of success and has identified serious issues which include *inter alia*: 1) use of faulty circular logic to prove the existence of the expressed antibody; 2) absence of critical controls to exclude artifactual explanations; 3) failure to detect the heavy chain in nearly

all experiments; and 4) contradictory and inconsistent results from immunogold labeling experiments. These issues, which have been discussed extensively in previous communications and are addressed again in this response (see below), have not been challenged by the Examiner. Furthermore, Dr. Lerner concludes from his analysis that a person skilled in the art of immunology or protein expression, circa 1988/1989, would not have reasonably believed the assertion of the During dissertation that plant cells could be used to process and assemble an antigen-specific immunoglobulin. See Lerner declaration, ¶ 22.

There is no reasoning in the Final Office Action that challenges any of Dr. Lerner's findings or conclusions. It cannot be denied that Lerner's concerns about During are serious and go to the very basis of During's alleged claim of success. It is improper for the Examiner to accept at face value the assertions of success by During, particularly in view of the Lerner Declaration. As already discussed, a prima facie rejection requires the identify all claim limitations in the combination of prior art teachings as well as rationale for a reasonable expectation of success and motivation to combine. The combination of prior art teachings also must be enabling. See Beckman Instruments, Inc. v. LKB Produkter AB, 892 F.2d 1547, (C.A.Fed. (Md.),1989) ("In order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method."). Because of these requirements, the Examiner is obligated to look to the substance of During's work, and in doing so, accord proper weight to the opinion of Dr. Lerner. The present rejection is most clearly deficient in this regard.

The rejection also is deficient because it fails to consider the view of the ordinary skilled artisan. The only view cited is that of the examiner's personal opinion. Applicants, however, have provided the opinion of Dr. Lerner and known expert in the field of immunology. As it currently stands, the weight of the evidence of record clearly supports that the claimed invention is not obvious over Goodman and During in view of Stolle.

The following is a further rebuttal of the rejection that address the teachings of the cited art in combination. For the benefit of the Examiner, Applicant will again address in detail the findings of the Lerner Declaration.

The state of the prior art

Applicants have previously established the state of the prior art with the filing of a declaration by Dr. Richard Lerner, an expert in the field of immunology. (see Lerner declaration filed March 13, 2002). Lerner addresses the view of the ordinary skilled artisan in the proper timeframe, the period beginning from the alleged publication date of the During dissertation (July 1988) and up to the earliest filing date of the above captioned patent application (October 27, 1989). His analysis shows that there is strong evidence at the relevant time period for the existence of a prejudice in the art against the possibility of using plant cells to process and assemble an antigen-specific immunoglobulin. According to Lerner, it was appreciated by the early 1980s that the biology of antibody expression was complex and varied with the maturation state of the B cell. For example, rearrangement of immunoglobulin chain variable region encoding gene segments is required to form a functional immunoglobulin gene, and rearrangement of the heavy chain occurs before rearrangement of the light chain. In fact, there is an early stage B cell known as the "pre-B cell," characterized in having a productively rearranged heavy chain V gene but not a rearranged light chain V gene. Lerner declaration, ¶3. In contrast, a later stage of B cells is known (i.e., "young B cell), characterized in having both the heavy and the light chain V genes productively rearranged and in expressing a full-sized immunoglobulin on the cell surface. *Id.*

Lerner goes on to explain that antibody expression in B cells was understood to be further complicated by the involvement of the BiP protein, known to be involved in heavy chain processing. Lerner declaration, ¶3. A phenomenon called heavy chain toxicity also was appreciated at the time but its mechanism was unknown. Lerner declaration, ¶4. According to Lerner, by the mid 1980s, a prejudice had taken hold in the art against the notion that antigen-specific immunoglobulins could be produced in cells other than mammalian B cells. *Id.*

Although Lerner notes the existence of reports describing expression of an assembled antibody in two microorganisms (i.e., *Saccharomyces cerevisiae* and *E. coli*) he provides substantial reasoning for why the prevailing prejudice in the art would still have

existed with respect to producing antigen-specific immunoglobulin in plant cells. Lerner declaration, ¶7. For example, Lerner notes that plant cells were known to be different from mammalian cells and from microorganisms such as *Saccharomyces cerevisiae* and *E. coli* not only in having a cell wall but also in features related to protein secretion. In addition, Lerner notes that it was not known at the time whether plant cells contained a BiP protein or a functionally equivalent analogue. Lerner concludes from his review of the field that:

> [T]here was a sound basis for a real prejudice in the art against using plants to produce a processed and assembled immunoglobulin which is antigen specific around the time of the During dissertation (*circa* 1988/1989). Were this not the case, then Applicant's invention clearly would not have been roundly hailed in both the scientific literature and in the general press as a significant scientific discovery and medical breakthrough.

Lerner declaration, ¶8 (footnotes removed).

Thus, the state of the art prior to October 27, 1989, leads to the conclusion that a person of skill in the field of immunology or protein expression would not have considered it possible to produce a functional antigen binding immunoglobulin in plant cells. Although During's dissertation concludes that successful antibody expression had been achieved in plants, the prevailing prejudice in the art necessitates a close inspection of the underlying science to determine if his conclusion is justified. As will be discussed below, the science underlying the dissertation is highly deficient and would not have convinced one of ordinary skill even in the absence of any prejudice and certainly not in view of the prejudice. This prejudice is relevant to the pending claims and should be taken into account when viewing the alleged achievements of Goodman, During and Stolle, discussed ahead.

Goodman et al.

Goodman et al., which as the primary reference has been cited for allegedly teaching the expression of an antigen specific immunoglobulin in plants, is notably

deficient in this regard. Goodman at most makes only passing reference to a desire to obtain immunoglobulins from plants but provides no teaching whatsoever for how to accomplish this goal. The only teaching of reference in Goodman is as follows:

> Structural genes of interest include α -, β - and γ - interferons, immunoglobulins, with the structural genes coding for the light and heavy chains and desirably assembly occurring in the plant cell, lymphokines, such as interleukins 1, 2 and 3, growth factors, including insulin-like growth factor, epidermal growth factor, platelet derived growth factor, transforming growth factor-α - β, etc., growth hormone, insulin, collagen plasminogen activator, blood factors, such as factors I to XII, histocompatibility antigens, enzymes, or other mammalian proteins, particularly human proteins

However, as already discussed, the claims require as a material limitation, plant cells containing nucleotide sequences encoding an immunoglobulin heavy chain polypeptide and an immunoglobulin light chain polypeptide wherein said nucleotide sequences also encodes a leader sequence for each polypeptide. Also required is antigen specific immunoglobulin product encoded by the nucleotide sequences, wherein each leader sequence forms a secretion signal that is cleaved from each of said immunoglobulin heavy chain and light chain polypeptides following proteolytic processing. Implicit in the claim is the requirement for assembly of heavy and light chains so as to form an antigen-specific immunoglobulin. Goodman fails to teach or suggest any of these clam limitations.

Goodman's teachings at best are limited to expressing gamma interferon, a lymphokine that is a single polypeptide and is functionally distinct from immunoglobulin. Goodman offers little if anything in the way of an enabling disclosure for expressing any heteromultimeric protein, let alone an immunoglobulin where both polypeptides need assemble to generate antigen specificity. For example, Goodman fails to discuss any of the factors that one should be aware of when attempting to obtain assembly of a functional multimeric protein. These factors include, for example,: 1) Methods for introducing the nucleic acid sequences encoding each of the polypeptides into the same host cell. Goodman is silent as to methods for co-transformation of multiple vectors or vectors containing more than one coding nucleic acid sequence; 2) Equivalent expression

of each polypeptide chain, produced in sufficient concentration, in the same cellular compartment. Goodman fails to teach transcriptional and translational requirements for expressing multimeric proteins, such requirements being significantly different from the requirements for expressing a single polypeptide. For instance, the promoters operatively linked to the nucleic acid sequences should insure that mRNA expression occurs at the same level; 3) Each polypeptide should have a functional leader sequence which is processed along the protein secretory pathway via proteolytic cleavage; and 4) Methods which allow the regeneration the transformed cell in a manner that ensures that both genes are retained during the process.

In view of the state of the art as discussed above, the meager description supporting immunoglobulin expression in Goodman would not have motivated others to believe that expression of an antigenic specific immunoglobulin was feasible in plants. The file history of the Goodman patent, which issued from U.S. application serial no. 760,236 filed July 29, 1985, also confirms this view. First, none of Goodman's original claims were directed to expressing immunoglobulin or for that matter any heterodimer in plants. Original claims of 760,236 are attached as EXHIBIT 1. Thus, the originally filed claims indicate that Goodman never seriously considered that his discovery could be extended to immunoglobulin. Furthermore, the Patent Office rejected Goodman's claims for lack of enablement because they extended to single polypeptides other than interferon, the only exemplified embodiment.

> Claims 1-5, 7, 8, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to Agrobacterium-mediated dicot transformation with chimeric genes comprising opine synthase promoters and structural genes encoding human interferon or antibiotic resistance as per pages 10-18. . . . Given the unpredictability inherent in the art, undue experimentation would be required by one of ordinary skill in the art to determine DNA sequences for non-disclosed mammalian peptides or promoters and to develop transformation vectors resulting in detectable expression of stable, bioactive peptides as claimed in claims 1-5, 8, 10 and 11.

U.S. serial No. 760,236, Office Action 6/9/87, pages 3-4 (Office Action attached as EXHIBIT 2). Goodman failed repeatedly to convince the examiner to withdraw the lack of enablement rejection and eventually appealed the case to the Board of Patent Appeals and Interferences. On September 29, 1989, the Board affirmed the rejection for non-enablement. The Board's decision makes clear as quoted below that the patent is not enabling for any mammalian peptide other than interferon.

> It appears to have been accepted by the examiner that the experimental portion of appellants' specification enables one of ordinary skill in the relevant art to repeat that which appellants have done, i.e., obtain the expression of an interferon gene through the use of a transformed Ti-plasmid in dicotyledonous plant cells. In view of the very same high order unpredictability of success in extrapolating reported procedures to different systems, e.g., different genes, different vectors, and different hosts, discussed above, appellants' arguments that their disclosure enables one of ordinary skill to practice the inventions claimed more generally in the broader claims without the exercise of undue experimentation are unreasonable on their face.

BPAI Decision, page 4-5 (BPAI decision attached as EXHIBIT 3). The position of the Board supports Applicants' view that Goodman does not enable expression in plants of any immunoglobulin.

The During Dissertation

It is respectfully submitted that the During dissertation falls far short of curing the many deficiencies in the primary reference with respect to the requirement for the material limitation of expressing an antigen-specific immunoglobulin in plants. The many scientific deficiencies of the During dissertation are discussed below. Indeed, the science underlying the During dissertation is substantially deficient and does not support the claim of success alleged by During.

A. The strategy for light chain and heavy chain expression adopted by During is unusual.

The During dissertation describes an attempt to co-express the heavy and light chains of an IgM antibody known at B1-8 in plants. The strategy was to encode a leader sequence in front of the codons for the mature antibody chains. For the heavy chain leader, During introduced nucleic acid encoding the barley alpha amylase signal sequence directly in front of (5' to) the DNA encoding the amino terminal end of the heavy chain.[2] During used the same amylase signal sequence for the light chain, but this time he included nucleic acid encoding three additional amino acids (Gly-Ser-Met) between the DNA encoding the leader sequence and the DNA encoding the amino terminus of the light chain. Lerner declaration, ¶9. During, therefore, used two distinct strategies for expressing each immunoglobulin chain.

The additional amino acids that would, through During's strategy, be encoded at the 3' end of the B1-8 light chain leader sequence were unusual in the context of known eukaryotic signal cleavage sites. Lerner declaration, ¶¶10 and 11. At the time of During's dissertation, it was not clear what effect additional amino acids at the end of a leader sequence would have on final processing of the leader. Studies by the present Applicants as well as others in the art indicate that by introducing the amino acids Gly-Ser-Met between the C-terminal end of the leader and the first amino acid of the mature kappa chain, the structure of the potential cleavage site is altered.[3]

It is now clear from the art that mutations introduced in the vicinity of a cleavage site can adversely influence signal processing. Lerner declaration, ¶11. This conclusion is based on analysis of many scientific reports, which address: 1) naturally occurring cleavage sites,[4] and 2) the effect of mutation on the function of a cleavage site.[5]

During's strategy for mating the light chain leader to the mature light chain sequence cleavage site may have resulted in cleavage site ambiguity. Lerner declaration,

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[2] Lerner Declaration, APPENDIX 2 (During dissertation), p18, top of page.

[3] Lerner Declaration, APPENDIX 15, (Nielsen et al., Protein Engineering, 10:1-6, 1997) see abstract).

[4] Lerner Declaration, APPENDIX 15-23 (See references and abstracts).

[5] Lerner Declaration, APPENDIX 24-38 (See references and abstracts).

¶¶11 and 12. This conclusion is based on statistical[6] and neural network[7] predictions of probable cleavage sites. For example, in all instances where Gly-Ser-Met is theoretically introduced distal to a cleavage site, an incorrect or absent cleavage site is predicted.[8], [9]

To Applicant's knowledge, nobody has ever reproduced During's work to determine for a fact that the light chain leader sequence is improperly processed when two polar amino acids (Gly-Ser) followed by a methionine residue are located in the cleavage site. However, a good deal of science supports but does not guarantee a conclusion that During's approach would have impaired light chain processing and, consequently, functional antibody production in his transformed plants.[10] Although this fact alone would not defeat During's conclusions if his expression data were solid, the use of an unusual cleavage site for the light chain is damaging because it is but one of many unanswered questions that raise serious doubts about the ultimate believability of the alleged conclusions of success.

B. During's experimental evidence allegedly supporting heavy and light chain processing and assembly of an antigen-specific immunoglobulin is inconsistent and lacking in critical controls.

The During dissertation describes that plant cells were initially transfected with DNA encoding the antibody light chain but not the heavy chain. It is important to note that During attempted but failed to detect light chain expression in the cells (During dissertation, p. 80, line 2).[11] The failure to detect expression of light chains would clearly

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[6] Lerner Declaration, APPENDIX 23 (See Von Heijne et al and abstract).

[7] Lerner Declaration, APPENDIX 15, (See Nielsen et al., and abstract).

[8] Lerner Declaration, APPENDIX 15 (See Nielsen et al, Center for Biological Sequence Analysis, Dept. of Biotechnology, The Technical University of Denmark website (www.cbs.dtu.dk/; SignalP cleavage site predictor).

[9] Lerner Declaration, APPENDIX 15 (See Nielsen et al., Protein Engineering, 10:1-6, 1997, (see abstract)); APPENDIX 39 (Duffaud et al., J. Biol. Chem., 263:10224-10228, 1988, (see abstract)).

[10] Lerner Declaration, APPENDIX 23 (See Von Heijne et al., (see abstract)).

[11] Lerner Declaration, APPENDIX 2 (During dissertation), p. 80, line 2 ("Repeated attempts to directly detect the light chain of B1-8 and for T4 lysozyme from the crude extract of tobacco mesophyll protoplasts were unsuccessful.").

have been disturbing to the ordinary skilled artisan because it was known that light chains can be readily expressed without heavy chains in B cells.

Furthermore, this fact would have raised serious concerns about the ultimate feasibility of achieving functional immunoglobulin because both chains are needed to assemble. The absence of a detectable light chain raises a lot of questions. For example, a very low level of light chain expression would make it that much more difficult to detect heavy-light chain assembly even if it had occurred to some very small extent. In addition, an excess of heavy chain resulting from poor light chain expression conceivably could be toxic if plant cells turned out to be susceptible to heavy chain toxicity phenomenon known at the time for mammalian B cells.[12] During responded to the problem by moving to assays with greater sensitivity, however, as will be seen below, During failed to include controls essential for working under these conditions.

During proceeded to clone the heavy chain with the light chain into a dual cassette expression vector and attempted to express both chains in plant cells. Page 86-95 of the During dissertation contains the results and discussion related to detection of antibody expression which employed Western blotting and tissue printing (see section 3.14, pages 86 to 90) as well as ultrastructural analysis of transfected plant tissue (see section 3.16, pages 92-95). As indicated by the statement below, During understood that his expression system was suboptimal, and that if assembled antibody were produced, the amount would be very low relative to the total protein.[13]

> Due to the expected level of low percentage of sought protein in the total protein, sensitive detection methods had to be developed. For this purpose , a non-radioactive detection system, which is compatible with the system for DNA hybridization described in 2.7.5 and 3.3, was worked out for detection of proteins on nitrocellulose and Immobilon filters. . .
>
> .
>
> A method therefore had to be developed that permits the sought protein to be enriched from the crude extract before

[12] Lerner Declaration, APPENDIX 3 (See Boyle et al).

[13] Lerner Declaration, APPENDIX 2 (During dissertation), p.86, 2nd to last paragraph and 4th paragraph of p. 87.

Western blot or preferably to be isolated and concentrated to detectable concentration.

The acknowledged deficiencies of During's expression system ultimately forced him to develop a pre-enrichment scheme in order to apply Western blotting. Lerner declaration, ¶14. Such scheme would have raised concern with the ordinary skilled artisan as to the overall credibility of During's findings because direct Western blotting was known to be extremely sensitive and had previously been used for demonstrating foreign host expression. *Id.* Indeed, in contrast to During's inability to use direct Western blotting, assembled antibody generated in tobacco plants using Applicant's system as described in the above-captioned patent application were readily detected by direct Western blotting (see Figure 5 of the above-captioned patent application). During's efforts to increase sensitivity created a greater potential for artifactual results, necessitating additional experimental controls. As will become evident below, During's experimental approach failed to include these critical controls.

To enrich for antibody in the plant extract prior to Western blotting, During exposed large volumes of plant extract to several rounds of affinity purification with CNBr activated Sepharose 4b to which is attached Ls136 antibody (monoclonal antibody allegedly specific for the light chain) or NP hapten.[14] Bound antibody (if present) was eluted, according to During, with 0.1 M glycine, pH 2.3 presumably for the Ls136-sepharose or NIP-cap for the NP-Sepharose.[15] During's Western blotting results are shown in Figure III/232 and discussed on page 89-90. The Examiner is referred to the Lerner declaration § 15 for details of During's indirect Western results.

During indicates that direct Western detection was unsatisfactory and that he could detect only "processed light chain" in the callus material through the pre-purified extracts.[16] During's statement appears to indicate that heavy chain detection was

[14] Lerner Declaration, APPENDIX 2 (During dissertation), p. 87, 4th full paragraph through page 89, lines 11-13

[15] Lerner Declaration, APPENDIX 2 (During dissertation), p.47, lines 7-10.

[16] Lerner Declaration, APPENDIX 2 (During dissertation), p89, lines 3-4

attempted, but was unsuccessful. This observation is based on the fact that During planned to detect heavy chain with an anti μ chain antibody by Western blotting[17] and because there were no results featured showing heavy chain detection. Thus, During failed to detect either the light or heavy chain in direct Western blotting but allegedly detected a "processed" light chain but not a heavy chain in the indirect (pre-processed) Western blots. Lerner declaration § 15

During's assertion that he has detected the presence of assembled B1-8 antibody in the plant cells is based, according to Lerner, on faulty circular logic.

> To conclude as he does from the Western results that assembled B1-8 antibody was present in the plant extract, During must infer that which he is attempting to prove, that fully assembled antibody must have been present in the extract for light chain to have been enriched following binding to the NP hapten immunoabsorbent. As will be seen below, this faulty circular reasoning is open to alternative explanations that directly conflict with During's conclusion.

Lerner declaration, ¶ 15.

Lerner goes on to discuss numerous other reasonable explanations for the results that During did not address, let alone attempt to exclude. See Lerner Declaration ¶ 15. During's assertion of successful heavy-light assembly in plants based on the western blotting experiments severely lacks the type of proof that would normally be required under the circumstances. Even accepting for the sake of argument During's detection of a "processed light chain" by indirect Western blotting, assembly of an antigen-specific immunoglobulin requires a heavy chain and During has no direct proof from either the direct or indirect Western that heavy chain was expressed in any reasonable amount. In fact, any of a number of artifacts may be the cause of During's Western results. For example, assuming for the sake of argument that a light chain was expressed by the plants, the NP hapten immunoabsorbents might have bound light chain in the absence of heavy chain expression during the "enrichment" procedure. This is a real possibility because light chains alone have been known to exhibit a reduced but detectable affinity

[17] Lerner Declaration, APPENDIX 2 (During dissertation), p.86, lines 12-13.

for antigen, particularly in circumstances such as the present case when the antigen is immobilized. Alternatively, light chains could have been purified by the immunoadsorbents if an endogenous plant protein existed which coincidentally had features in common with the heavy chain of the B1-8 antibody.

Although Applicants have no direct evidence that any of these scenarios were at play, During should (and could) have eliminated them by employing any of a number of possible controls. For example, During could have directly demonstrated that heavy chain was absolutely required for light chain binding in the pre-enrichment step. Alternatively, or in addition, During could have used biosynthetic radiolabeling of plant cells in combination with Western blotting to prove that a heavy chain was in fact co-enriched with light chain. This method is well known in the art and was previously used to demonstrate foreign protein expression.[18] Biosynthetic radiolabeling also would have helped to control for stripping of antibody during a low pH elution of an antibody immunoabsorbent column (i.e., the Ls136 adsorbent), a problem encountered with CNBr.[19] Since During employed low pH elution and CNBr linkage, he should have provided controls to address this potential problem.[20]

Thus, although there was much that During could have done in the way of controls to support the conclusions he drew from his Western blotting results, the decision not to run the critical controls raises serious doubts about what conclusions should properly be drawn from these data. Lerner declaration, ¶ 16.

During also evaluated antibody expression using "tissue printing," in which a leaf is pressed against a membrane in order to bind various proteins in the leaf to the membrane and the membrane is probed by the various immunological reagents used in Western

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[18] Lerner Declaration, APPENDIX 40 (See e.g., Rothstein et al., Nature, 308:662-665, 1984, Fig. 2 (expression of wheat α-amylase in yeast cells labeled with ^{35}S-methionine).

[19] Lerner Declaration, APPENDIX 41 (See Lihme et al., J. Chromatography, 376:299-305, 1986, table 1).

[20] Ls136 antibody which may have leached into the "enriched" leaf extracts may be detected by cross reaction with the secondary reagents in the western blot.

blotting.[21] No extract is made in this case and no enrichment is used. In these experiments, During allegedly detected light chain, heavy chain and "aggregated B1-8," (the latter conclusion presumably is a result of Ac38 antibody binding to the tissue print). It is disturbing that During never even attempted to explain why heavy chain was detected in these experiments but not in the Western blots. In any event, even if he could explain this discrepancy in a scientifically acceptable manner, the tissue printing experiment inexplicably lacks the type of controls that are normally required for this experiment. Lerner declaration, ¶ 17. The controls needed for tissue printing are the same types of controls typically employed in antibody binding assays such as ELISA or immunohistochemistry. As is always the case for antibody reagents (polyclonal or monoclonal), one **must** use antigen inhibition to properly validate the specificity of binding in each assay format (i.e. that binding is "antigen-specific").[22] Lerner declaration, ¶ 17. Lerner bases this view not only on his own experience as a scientist and immunologist for more than 30 years but also on the scientific literature. With respect to the latter, Lerner points out that the types of controls lacking in the During dissertation were used by others who previous to During demonstrated expression in yeast of the same B1-8 antibody that During was attempting to express in a plant.

For example, Gubler et al. demonstrated α-amylase secretion by plant cells by inhibiting tissue staining with antigen.[23] Similarly, Wood et al. used antigen inhibition to demonstrate B1-8 antibody assembly in yeast (the same antibody used by During).[24] In fact, Wood demonstrated that the NIP form of antigen inhibited better than the NP form of hapten, a well known signature of the B1-8 antibody.[25] The During dissertation evidences

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[21] Lerner Declaration, APPENDIX 2 (During dissertation), paragraph bridging p.88 and 89.

[22] Antigen inhibition arguably might not be needed if antibody detection were only one of several assays used immunoglobulin expression. However, During relied solely on immunological detection.

[23] Lerner Declaration, APPENDIX 42 (See Gubler et al., Planta, 168:447-452, 1986, pl448, right hand column (Specificity of antibody staining evaluated by using antibody previously absorbed with a 50 fold excess of antigen).

[24] Lerner Declaration, APPENDIX 10 (Wood et al., p448, right hand column, middle of page).

[25] Lerner Declaration, APPENDIX 10 (Wood et al., APPENDIX 10, p448, right hand column, middle of page).

that During was aware of the Wood et al. reference[26] and the heteroclitic nature of the B1-8 antibody,[27] but for reasons unknown, During failed to conduct any antigen inhibition controls. Sossountzov et al. studying immunogold localization of abscisic acid in plant tissues of *chenopodium polyspermum L*, likewise used an antigen inhibition control, which the authors recognized as vital (emphasis added to the following quote).[28]

> Preabsorbed ABA antibodies, **which constitute an essential control for determining the specificity of the immunolabelling**, produced less than one gold particle per μm^2 over cytoplasm, nucleic and plastids.

Although During diluted his antibody reagents with wildtype plant extract and still observed binding, this control is not sufficient to exclude other artifacts. For example, binding directed to insoluble antigens not present in the extract would not be inhibited in the presence of the extract.

Thus, although the tissue printing experiments were easy to do, During again failed to perform critical controls necessary to support the conclusions he drew from the work. During's use immunological detection without proof of antigen specificity is a fatal flaw to any conclusion of success.

The During dissertation includes immunogold electron microscopic analysis of the plant cells containing the dual heavy and light chain vector apparently using the same antibody reagents used in the Western blotting and tissue printing experiments. The Examiner is referred to the Lerner declaration § 18 for a detailed explanation of During's immunogold results. The dissertation describes that the Ac38 antibody (allegedly specific for a properly assembled B1-8 antibody) reacted with endoplasmic reticulum (ER) and chloroplasts in cells from induced plant stems.[29] Also described is that the Ls136 antibody (allegedly specific for light chains), reacted with cytoplasm, but not with ER or

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[26] Lerner Declaration, APPENDIX 2 (During dissertation), p.17, first full paragraph.

[27] Lerner Declaration, APPENDIX 2 (During dissertation), p.86, lines 21-23.

[28] Lerner Declaration, APPENDIX 43 (Sossountzov et al, Planta, 168:471-481, 1986, (p. 480, left hand column)).

[29] Lerner Declaration, APPENDIX 2 (During dissertation) p. 94, first full paragraph ("Each chloroplast contains about 23-30 gold particles, often localized on thylakoid membranes").

chloroplasts.[30] Further described is the observation that none of the antibody reagents labeled in the vicinity of the plant cell wall or the intercellular space, and that no reaction with the golgi apparatus or vesicles were seen.[31] During concludes without explanation that these experiments indicate "synthesis and assembling of a monoclonal B1-8 antibody . . . occur [sic] in the plant cells on the rough ER . . . "[32] If During's conclusion about successful B1-8 assembly in plant cells was correct, the Ac38 immunoreactivity would mean that assembled antibody, i.e., both a light chain and a heavy chain, were present in the ER and chloroplasts.

Such conclusion, however, conflicts with During's failure to observe light chain immunogold labeling of ER or chloroplasts. Lerner Declaration, ¶ 18. Furthermore, the chloroplastic reactivity by the Ac38 antibody is perplexing and During provided no explanation for why allegedly assembled antibody would be concentrated in this organelle[33] Lerner notes that only weak immunogold labeling of chloroplasts was observed in During's plant cells expressing T4 lysozyme.[34] Adding further to these deficiencies is During's failure to detect any heavy chain in the immunogold labeling experiments.

Lerner takes issue with During's conclusion that the immunogold results indicate successful assembly of the B1-8 antibody in plants. First, Lerner notes that the heavy chain again was not detected and because areas of the cell that were immunogold labeled with the light chain reagent were not the same areas that were immunogold labeled with the Ac38 reagent (allegedly specific for assembled B1-8). Lerner declaration, ¶ 18. It stands to reason that for assembly to have occurred, the two chains should be co-localized to at least one area of the cell. However, no such co-localization as observed by

[30] Lerner Declaration, APPENDIX 2 (During dissertation) p.94, lines 7-10.

[31] Lerner Declaration, APPENDIX 2 (During dissertation) p.94, lines 10-12.

[32] Lerner Declaration, APPENDIX 2 (During dissertation) p.94, last paragraph.

[33] Chloroplastic targeting was known to require a special amino terminal transport peptide, something which to my knowledge has not been demonstrated in antibodies. Chloroplastic immunoreactivity was observed for abscisic acid but this is not a protein (see Sossountzov et al., Lerner Declaration, APPENDIX 43).

[34] Lerner Declaration, APPENDIX 2 (During dissertation), p.97, line 1.

During. Furthermore, During failed to observe immunogold labeling in regions of the cell where normally would have expected antibody assembly to occur if assembly were in fact possible in plant cells. Lerner declaration, ¶ 19. Indeed, During observed immunoreactivity inexplicably in chloroplasts with the Ac38 antibody but not in the golgi apparatus or vesicles as others have observed previously for secreted proteins including antibodies. Unusual results might be acceptable if plant cells were capable of antibody assembly in unique and previously unknown ways. However, when critical controls are lacking, unusual results further detract rather than support any conclusion that can reasonably be drawn from the results.

Lerner further takes issue with the reliance During places on the Ac38 antibody to support his conclusions from the immunogold labeling highlights. See Lerner declaration, ¶ 20. The Ac38 antibody reacts with the Ac38 idiotype, an antigenic determinant expressed on cell surface immunoglobulin in the B cell population of C57BL/6 mice at very high frequency (around 1/1,000).[35] It was known, however, in the early 1980s that the majority of Ac38 idiotype bearing antibodies induced in C57BL/6 mice (by immunizing with Ac38 antibody) do not have NP binding specificity.[36] This means that Ac38 antibody binding cannot be used to claim that NP antigen binding specificity is present, even if Ac38 binding were proven to be Ac38 idiotype specific by inhibiting binding with the specific antigen. Thus, even if During had done the proper antigen inhibition controls, he still could not use Ac38 antibody binding to infer that B1-8 light chain and heavy chain were properly processed and assembled resulting in NP antigen specificity. Thus, During has failed to demonstrate that any immunoglobulin that might have been assembled from heavy and light chain (assuming arguendo that both chains were produced) was in fact antigen-specific.

The During dissertation concludes that the ultrastructural immunogold results support the Western blotting results which together demonstrate synthesis and assembly

[35] Dildrop et al., EMBO, 3:517-523, 1984, APPENDIX 45, p.517, right hand column.

[36] Dildrop et al., APPENDIX 45, p517, right hand column ("The resulting Ac38-positive hybridomas are thus in the majority unreactive with the NP hapten.").

of a monoclonal antibody in plants.[37] However, as amply demonstrated and supported by the declaration of Dr. Lerner, During's conclusion of success is wholly unwarranted in view of the experimental difficulties such as the failure to detect the B1-8 heavy chain, and the lack of proper controls.

C. During's conclusion of successful antibody expression would not have been believed

Lerner concludes that a person skilled in the art of immunology or protein expression, circa 1988/1989, would not have reasonably believed the assertion of the During dissertation that plant cells could be used to process and assemble an antigen-specific immunoglobulin. Lerner declaration, ¶ 22. Lerner bases this opinion on During's failure to perform critical controls to support his conclusions and to explain his inconsistent results. Also, the Ac38 antibody which underlies virtually all of the support for During's assertion cannot be used, according to Lerner, to prove that antigen specific immunoglobulin was produced in plant cells. Lerner declaration, ¶ 22. Thus, even if During had done the proper antigen inhibition controls, much more would have been needed, according to Lerner, to overcome the prejudice in the art. *Id.*

The During dissertation alone or in combination with Goodman does not overcome this prejudice because it has serious unexplained inconsistencies and lacks critical controls. The following experimental deficiencies with the During Dissertation were addressed above:

1. Faulty circular logic was employed to prove the existence of the B1-8 antibody;

2. Critical controls were not used allowing for artifactual explanations;

3. Heavy chain could not be detected; and

4. Immunogold labeling was contradictory and inconsistent with what as known about antibody processing and assembly.

These four deficiencies all go to the critical question of what was actually detected by During in his assay. It is respectfully submitted that absence of critical controls is

[37] During dissertation, APPENDIX 2, p.94, last paragraph.

highly germane to whether During's assay could have detected the expressed antibodies. This is particularly so in the case where there were experimental failures and where one is pushing detection to the outer edge.

It is also Lerner's opinion that even if there were no prejudice in the art, During's conclusions would still not have been accepted. This view is based in part on Lerner's extensive experience as an editorial board member of more than ten scientific journals and an official reviewer for hundreds articles submitted for publication. Even in its best light, giving the During dissertation the full benefit of the doubt, the skilled artisan would still not have believed During's claims of immunoglobulin assembly in plant cells.

Although During eventually published his antibody work in a peer-reviewed journal (i.e., Plant Molecular Biology), this occurred after the inventors of the above-captioned application published their work (1989 Nature article). Furthermore, as noted by Lerner, During's publication discusses the earlier publication by the inventors Hiatt and Hein at some length, describing it as a successful demonstration of antibody expression in plants. Lerner declaration, ¶ 22. In Lerner's opinion, had During not been able to support his work with the earlier publication by Hiatt and Hein, During's antibody expression experiments most likely would have been deemed unacceptable for publication. Lerner credits the inventors of the instant patent application, not During, as the first to convincingly demonstrate assembly of an antigen-specific immunoglobulin in plant cells.

Although During was awarded a Ph.D. degree for his dissertation, which presumably was subject to a reviewing committee at the University of Koln, one cannot know what weight the dissertation committee gave to his antibody expression experiments versus the T4 lysozyme expression experiments. Lerner declaration, ¶ 22.

It is respectfully submitted that the During dissertation falls far short of curing the deficiencies in the teachings of the Goodman patent. Like that of Goodman, During fails to enable the material limitation of the claims for plant cells containing nucleotide sequences encoding an immunoglobulin heavy chain polypeptide and an immunoglobulin light chain polypeptide wherein said nucleotide sequences also encodes a leader sequence for each polypeptide. During uses leader peptides, but it is unclear whether he used them

properly as the data do not show clear evidence of immunoglobulin expression. During also fails to convincingly demonstrate plant cell production of antigen-specific immunoglobulin product encoded by the nucleotide sequences, wherein each leader sequence forms a secretion signal that is cleaved from each of said immunoglobulin heavy chain and light chain polypeptides following proteolytic processing. As already discussed, During's use of the Ac38 antibody does not allow him to conclude that antigen-specific antibody was ever produced.

Stolle et al.

Stolle et al., does not cure any of the deficiencies of the primary or secondary references already discussed. Stolle et al. does not even mention, let alone teach how to prepare antigen-specific immunoglobulin in plant cells. Stolle et al. also does not describe the requirement for the transgenic nucleic acid to encode a leader sequence and for the leader sequence form a secretion signal which is cleaved from the immunoglobulin polypeptide (heavy or light chain) following proteolytic processing. Indeed, the only immunoglobulins described in Stolle et al. are obtained from conventionally immunized birds (see col.7, lines 40-51). Stolle et al. also does not cure the lack of believability of the During dissertation and its failure to convincingly prove production of antigen-specific immunoglobulin.

Thus, the rejection over Goodman and During in view of Stolle does not disclose or enable the claimed methods. Not only is the combination of art deficient for failing to teach or suggest all limitations of the claimed invention in an enabling manner, the rejection also is deficient in failing to establish that such combination in any event provides a reasonable expectation of success. As best as Applicants can determine, the alleged basis for a reasonable expectation of success cited in the Office Action is that both Goodman and During teach the expression of biologically active antibodies in transgenic plant cells, and that it would have been reasonable to combine their teachings with Stolle which teaches passive immunization albeit with conventionally made

antibodies. As will be shown below, this reasoning is in conflict with the facts and with positions taken by the examiner.

First, as already discussed and extensively addressed by Dr. Richard Lerner, the During dissertation is not credible and its findings would not have been accepted by those skilled in the art. In fact, this view has not been refuted or even challenged by the examiner. Thus, there simply cannot be a reasonable expectation of success when one of the references would have been adjudged a failure by the ordinary skilled artisan at the relevant point in time.

Furthermore, as argued many times by Applicants, Goodman's one sentence assertion that one can produce immunoglobulins in plants amounts to nothing when viewed in light of the prejudice in the art and During's many failures. Although During adds many experimental details lacking in Goodman, the combination fails to reach all the claimed limitations, lacks enablement and fails to provide a reasonable expectation of success, particularly in view of the prejudice in the art which an established fact in this case.

Because the cited art, alone or in combination fails to teach or suggest the instantly claimed methods, and because no motivation has been established for the modifications proposed by the Examiner, Applicant respectfully submits that no prima facie case of obviousness has been established. Applicant therefore requests that the rejection under 35 U.S.C. §103 be reconsidered and withdrawn.

Conclusion

Applicants have endeavored to fully address all arguments upon which the instant obviousness rejection is based. Various issues raised by the Examiner have been fully addressed. It is submitted that any one of these deficiencies is fatal to the rejection. However failure on all five bases demonstrates that the rejection is without basis and should be withdrawn.

Atty. Dkt. No.: EPI3007F
(formerly TSRI 184.2C2)

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is urged to contact the undersigned by telephone to address any outstanding issues standing in the way of an allowance.

Respectfully submitted,

Date August 11, 2003

By Barry Wilson

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WHAT IS CLAIMED IS:

1. A method for producing a mammalian peptide which comprises:

growing plant cells containing an integrated sequence comprising,

a first expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plant cells, (2) a structural gene coding for said mammalian peptide, and (3) a termination region,

whereby said structural gene is expressed to produce said mammalian peptide; and

isolating said mammalian peptide substantially free of plant cell components.

2. A method according to Claim 1, wherein said integrated sequence ~~includes~~ comprises a second expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plants, (2) a structural gene coding for a peptide which allows for selection of plant cells expressing said peptide, and (3) a termination region.

3. A method according to Claim 2, wherein said transcriptional and translational initiation region of said first expression cassette is derived at least in part from a transcriptional and translational initiation region of a Ti- or Ri-plasmid.

4. A method according to Claim 3, wherein said transcriptional and translational initiation region of said first expression cassette regulates expression of mannopine synthase, octopine synthase or nopaline synthase.

5. A method according to Claim 1, wherein said transcriptional and translational initiation

EXHIBIT 1

region of said first expression cassette regulates expression of a plant gene.

6. A method according to Claim 1, wherein said integrated sequence ~~includes~~ comprises a boundary region from T-DNA.

7. A method for producing an interferon which comprises:

growing plant cells containing an integrated sequence comprising,

a first expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plant cells and derived from a region which regulates expression of a T-DNA gene, (2) a structural gene coding for an interferon, and (3) a termination region functional in said plant cells,

whereby said structural gene is expressed to produce said interferon, and

isolating said interferon substantially free of plant cell components.

8. A method according to Claim 7, wherein said integrated sequence ~~includes~~ comprises a second expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plant cells, (2) a structural gene coding for an enzyme which imparts antibiotic ~~resistance~~, and (3) a T-DNA boundary.

9. A method according to Claim 8, wherein said first expression cassette transcriptional and translational initiation region regulates expression of the mannopine synthase gene of T-DNA.

10. An expression cassette comprising a DNA sequence having in the direction of transcription a transcriptional and translational initiation region functional in plant cells, a structural gene coding for a mammalian peptide, and a termination region functional in plant cells.

11. An expression cassette according to Claim 10 including joined to said DNA sequence a second expression cassette comprising a second transcriptional and translational initiation region functional in plant cells, a structural gene coding for a peptide providing a phenotypic property capable of selection in plant cells, and a termination region functional in plant cells.

12. An expression cassette according to Claim 11, ~~including~~ comprising a T-DNA boundary.

13. A DNA construct comprising a first expression cassette having in the direction of transcription a transcriptional and translational initiation region regulating the expression of mannopine synthase of T-DNA, a structural gene coding for γ-interferon and a termination region functional in plant cells, a second expression cassette comprising in the direction of transcription a transcriptional and translational initiation region regulatory the expression of octopine synthase of T-DNA, a structural gene coding for an enzyme imparting antibiotic resistance to plant cells, and a termination region functional in plant cells, and a T-DNA boundary.

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127	7

DATE MAILED: 06/09/87

This is a communication from the examiner in charge of your application.

COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 3/3/87 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-13 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-13 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.

8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).

10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____, has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved, ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.

12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

EXHIBIT 2

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an enabling disclosure.

The invention employs novel plasmids and microorganisms. Repeatability of the disclosed method and availability of starting materials is unclear; therefore a deposit should be made for enablement purpose.

Applicants may provide assurance of compliance with the requirements of §112 in the form of a declaration averring that (a) during the dependency of this application, access to the invention will be afforded to one determined by the Commissioner upon request, (b) all restrictions upon availibility to the public will be irrevocably removed upon granting of the patent and (c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer. See MPEP 608.01(p)C.

Claims 1-13 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the above objection to the specification.

Claims 1-5, 7, 8, 10 and 11 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to Agrobacterium-mediated dicot transformation with chimeric genes comprising opine synthase promoters and structural genes encoding human interferon or antibiotic resistance as per pages 10-18. See MPEP 706.03(n) and 706.03(z).

The specification only provides detailed experimental examples demonstrating dicot transformation using Agrobacterium. Other means of plant transformation are limited by lack of chromosomal incorporation of DNA and lack of plant regeneration from transformed protoplasts. Agrobacterium-mediated transformation is limited by host range and regenerability of transformed protoplasts to the dicots (Goodman et al. pages 52-53). Undue experimentation would be required by one of ordinary skill in the art to obtain non-Agrobacterium mediated transfer of monocots as claimed in claims 1 and 7.

Furthermore, the specification only provides detailed experimental examples demonstrating the expression of human interferon in plant cells regulated by opine synthase promoters. As admitted by Applicants (page 5 of Amendment filed on February 23, 1987) the ability of a given promoter to direct translation of a detectable amount of stable, bioactive, recoverable gene product is not predictable. For example, phaseolin

expression was virtually undetectable in transformed sunflower cells under phaseolin promoter regulation but was detected at significantly higher levels when regulated by the octopine synthase promoter (Murai et al, page 480, third column, first full paragraph). Given the unpredictability inherent in the art, undue experimentation would be required by one of ordinary skill in the art to determine DNA sequences for non-disclosed mammalian peptides or promoters and to develop transformation vectors resulting in detectable expression of stable, bioactive peptides as claimed in claims 1-5, 8, 10 and 11.

Claims 1-4, 6-8, 12 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 7 are incomplete for failing to include the means of introducing the claimed integrated sequences into the plant cells. Claims 2, 6, 8 and 12 are indefinite in their recitation of "includes" or "including" as it is unclear whether this is an open or closed term. Claims 3 and 4 are confusing in their recitation of "said transcriptional and translational initiation region" for failing to distinguish between the regions of the first or second expression cassette.

Claims 3 and 7 are indefinite in their recitation of "derived ... from" which fails to adequately characterize the claimed regions. Claim 4 is indefinite for failing to employ proper Markush terminology. See MPEP 706.03y. Claim 13 is confusing in its recitation of "regulatory the expression of" as it is unclear what Applicants intend.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-4, 6-8 and 10-13 are rejected under 35 U.S.C. 103 as being unpatentable over Murai et al in view of Gray et al.

Murai et al. discloses the recovery of phaseolin from sunflower cells transformed with chimeric genes comprising structural genes encoding phaseolin and a

selectable antibiotic resistance enzyme regulated by octopine synthase promoters. Gray et al. discloses the recovery of biologically active human interferon from E. coli and monkey cells transformed with cDNA encoding interferon. In the absence of unexpected results it would be obvious to one of ordinary skill in the art to incorporate the interferon-encoding cDNA disclosed by Gray et al. into the plant transformation method disclosed by Murai et al to obtain the claimed methods and expression cassettes, since the disclosed plant transformation vectors and cDNA would continue to function in their known and expected manner.

Claim 5 is rejected under 35 U.S.C. 103 as being unpatentable over Murai et al in view of Gray et al as applied to claims 1-4, 6-8 and 10-13 above, and further in view of Herrera-Estella et al.

Murai et al taken in view of Gray et al discloses a method for recovering interferon from plants as discussed supra. Herrera-Estella et al. discloses plant transformation using the pea RUBISCO small subunit promoter to recover bacterial enzymes conferring antibiotic resistance. In the absence of unexpected results it would be obvious to one of ordinary skill in the art to incorporate the promoter disclosed by Herrera-Estrella et al. into the transformation method disclosed by Murai

et al taken in view of Gray et al, since the RUBISCO promoter would continue to function in its known and expected manner.

Claim 9 is rejected under 35 U.S.C. 103 as being unpatentable over Murai et al in view of Gray et al as applied to claims 1-4, 6-8 and 10-13 above, and further in view of Velten et al.

Murai et al taken in view of Gray et al discloses a method for recovering interferon from plants as discussed supra. Velten et al. discloses the use of the agropine (mannopine) promoter in plant transformation to recover bacterial enzymes encoding antibiotic resistance. In the absence of unexpected results it would be obvious to incorporate the promoter disclosed by Velten et al. into the transformation method disclosed by Murai et al taken in view of Gray et al. since each would continue to function in their known and expected manner.

Any inquiry concerning this communication should be directed to David T. Fox at telephone number 703-557-3920.

DTF

FOX:wdh

6/4/87

THOMAS G. WISEMAN
SUPERVISORY PATENT EXAMINER
ART UNIT 127

TO S. ATE. O TOP AND BOTTOM EDGES, SNAP-APART ANC ARD CARBON

FORM PTO-892 (REV. 3-78) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED	760,236	127	7
	APPLICANT(S) Goodman et al.		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
	D						
	E						
	F						
	G						
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	I						
	J						
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FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

14	R	Velten et al. 1984. EMBO J 3(12): 2723-2730
14	S	Murai et al. 1983. Science 222: 476-482
14	T	Gray et al. 1982. Nature 295: 503-508
14	U	Goodman et al. 1987. Science 236: 48-54

EXAMINER	DATE
David T. Fox	5/23/07

* A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).)

TO S... ATE, ... TOP AND BOTTOM EDGES, SNAP-APART AND ...ARD CARBON

FORM PTO-892 (REV. 3-78) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED	760,236	127	7
	APPLICANT(S) Goodmcen et al.		

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	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

R	Herrera-Estrella et al. 1984. Nature 310: 115-120
S	
T	
U	

EXAMINER	DATE
David J. Aft	5/23/07

* A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).)

Art Unit 184

MAILED

Paper No. 15

Appeal No. 89-0918

SEP 28 1989

vgb

ON BRIEF

PAT. & T.M. OFFICE
BOARD OF PATENT APPEALS
AND INTERFERENCES

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte Robert M. Goodman
Vic C. Knauf
Catherine M. Houck
and
Luca Comai

- - -

Application for Patent filed July 29, 1985, Serial No. 760,236. Mammalian Peptide Expression in Plant Cells.

Bertram I. Rowland et al. for appellants.

Supervisory Primary Examiner - Charles F. Warren.
Examiner - D. Fox.

Before Goldstein, W. Smith and Haight, Examiners-in-Chief.

Goldstein, Examiner-in-Chief.

This appeal is from the examiner's final rejection of claims 1 to 13. There are no allowed claims. Illustrative claims 1, 7 and 8 are reproduced below.

1. A method for producing a mammalian peptide which comprises:

growing plant cells containing an integrated sequence comprising,

a first expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plant cells, (2) a structural gene coding for said mammalian peptide, and (3) a termination region,

whereby said structural gene is expressed to produce said mammalian peptide, and

EXHIBIT 3

isolating said mammalian peptide substantially free of plant cell components.

7. A method for producing an interferon which comprises,

growing plant cells containing an integrated sequence comprising,

a first expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plant cells and derived from a region which regulates expression of a T-DNA gene, (2) a structural gene coding for an interferon, and (3) a termination region functional in said plant cells,

whereby said structural gene is expressed to produce said interferon, and

isolating said interferon substantially free of plant cell components.

8. A method according to Claim 7, wherein said plant cells are dicotyledon plant cells and said integrated sequence comprises a second expression cassette having in the direction of transcription (1) a transcriptional and translational initiation region functional in said plant cells, (2) a structural gene coding for an enzyme which imparts antibiotic resistance, and (3) a T-DNA boundary.

References relied upon by the examiner on appeal are:

Gray et al. (Gray), Nature, Vol. 295, February 1982, pages 503-508.

Murai et al. (Murai), Science, Vol. 222, November 1983, pages 476-482.

Herrera-Estrella et al. (Herrera-Estrella), Nature, Vol. 310, July 1984, pages 115-120.

Velten et al. (Velten), The EMBO Journal, Vol. 3, No. 12, 1984, pages 2723-2730.

Goodman et al. (Goodman), Science, Vol. 236, April 1987, pages 48-54.

Reference of record discussed in the following opinion:

Shaw et al. (Shaw), "A General Method for the Transfer of Cloned Genes to Plant Cells," Gene, Vol. 23, No. 3, 1983, pages 315-330.

All of the appealed claims have been finally rejected under either or both of 35 USC 103 and 112. There have been some clear errors in keeping track of which claims were subject to

exactly which grounds of rejection throughout the prosecution of this application. However, it is clear that these inadvertent errors have not clouded the issues, which have been clearly defined by both the examiner and appellants on the record. The claims which, in our view, correspond to the different grounds of rejection based on the correspondence of the claimed subject matter to the issues raised by the rejection in each case are as follows.

With respect to the rejection under 35 USC 103 for obviousness, claims 1 to 4, 6 to 8 and 10 to 12 have been rejected as being unpatentable over the combined teachings of Murai and Gray. Herrera-Estrella has been considered additionally with respect to claim 5, and Velten has been considered additionally with respect to claims 9 and 13. The situation with regard to the rejection over prior art is simplified by appellants' acknowledgement that patentability of all of the claims rests on the unobviousness of the broadest claims over the basic combination of Murai and Gray.

The basis of the rejection under 35 USC 112 for lack of an enabling disclosure is the failure to specify the mammalian gene to be expressed, the vector for its expression and (in the process claims) the host in which the vector operates. In the final rejection, all three of these criteria were considered together. In the answer on appeal, the examiner has stated two separate rejections, one limited to the specific gene and the other limited to the vector and host. Since we agree with the examiner's position with regard to all three limitations, we shall simply distinguish those claims which recite all three (or, in the case of the "construct" or "expression cassette" claims, the two relevant ones) from those which do not, i.e., we shall treat the two rejections as one, in the manner of the final rejection. Thus, the claims which are subject to the rejection under 35 USC 112,

because they do not recite all of the essential limitations, are claims 1 to 7 and 10 to 12. The claims which are free of this rejection are claims 8, 9 and 13. To illustrate this distinction, we have above reproduced claim 8 together with claim 7, from which it depends, and claim 1.

With respect to the rejection under 35 USC 103, we find appellants' arguments convincing of error on the part of the examiner. The state of the art illustrated on this entire record, including the discussion of the prior art in the original specification as filed, the references now relied on by the examiner and all of the additional references of record, is clearly such that motivation existed to do that which appellants have done and here claimed. The evidence also illustrates that success has been achieved in performing related but not identical biotechnological syntheses. A nonmammalian eukaryotic gene has been expressed in a plant cell (Murai). A mammalian gene has been expressed in a eukaryotic animal cell, but not a plant cell (Gray). However, the only report before us concerning the expression of a mammalian gene in cells of higher plants is the Shaw article, which reports the transfer of the mammalian gene to the plant genome but failure to obtain expression, which apparently failed at the transcription stage (see the last sentence of the summary).

The examiner has failed to indicate how, from the prior art evidence of record, one of ordinary skill in the relevant art would have known what modifications to make in the various prior art procedures to obtain a result different from that reported in the Shaw article for example. In the absence of such an explanation, we find that appellants' claims would not have been obvious under 35 USC 103 based on this record and the examiner's explication thereof.

We shall affirm the examiner's rejection of claims 1 to 7, and 10 to 12 under the first paragraph of 35 USC 112.

It appears to have been accepted by the examiner that the experimental portion of appellants' specification enables one of ordinary skill in the relevant art to repeat that which appellants have done, i.e., obtain the expression of an interferon gene through the use of a transformed Ti-plasmid in dicotyledonous plant cells. In view of the very same high order of unpredictability of success in extrapolating reported procedures to different systems, e.g., different genes, different vectors and different hosts, discussed above, appellants' arguments that their disclosure enables one of ordinary skill to practice the inventions claimed more generally in the broader claims without the exercise of undue experimentation are unreasonable on their face.

From the arguments presented by appellants in their brief on appeal, it appears that they have also taken the more extreme position that no amount of experimentation would be undue and that, having carried out one successful, specific biosynthesis, they are per se entitled to claim the entire concept disclosed as a research goal in the prior art of record.

The factors to be taken into consideration in determining whether or not the amount of experimentation required to practice the subject matter of a patent claim is unduly burdensome under 35 USC 112 have been discussed at great length in reported prior decisions. See, for example, Ex parte Forman, 230 USPQ 546 (BPAI 1986); Ex parte Jackson, 217 USPQ 804 (Bd. App. 1982). We shall not burden the present record with a repetition of that entire discussion here. It is amply clear from appellants' arguments that they have not taken cognizance of those factors. They have expressed their opinion that it is not necessary to enable one of ordinary skill in the relevant art "to avoid the expenditure of sweat and monies which applicants expended at a time

when they could not be certain of success" (brief on appeal, page 8) and that it is acceptable to require those of ordinary skill, in practicing the invention, "to carry out the peeling of onions, the cutting of meat and the preparing of stew in order to have the dinner" (brief on appeal, page 8). These statements are entirely antithetical to the policy expressed in the enablement requirement of 35 USC 112. In the present case, appellants have emphasized the "high degree of unpredictability of success" in modifying specific known procedures in this field (brief on appeal, page 21), and nowhere on this record can one find any indication of what specific modifications of the Shaw process, for example, were responsible for appellants' success relative to the incompletely satisfactory results obtained by Shaw. Thus, their position on the issue of undue experimentation is particularly untenable on this record.

The examiner's rejection of claims 1 to 7 and 10 to 12 is affirmed. The rejection of claims 8, 9 and 13 is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR 1.136(a). See the final rule notice, 54 F.R. 29548 (July 13, 1989), 1105 O.G. 5 (August 1, 1989).

AFFIRMED-IN-PART

Melvin Goldstein)
Examiner-in-Chief)

William F. Smith)
Examiner-in-Chief) BOARD OF PATENT APPEALS AND INTERFERENCES

James C. Haight)
Examiner-in-Chief)

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